## DETAILED ACTION

Note to Applicant: References to paragraphs in non-patent literature refer to full paragraphs (e.g. 'page 1 column 1 paragraph 1' refers to the first full paragraph on page 1 in column 1 of the reference)

### *Status of Prosecution*

In order to introduce new grounds of rejection, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below. Briefly, the existing rejections are repeated that give weight to the method by which the polymer layer is formed by surface-initiated polymerization. However, it has not been established that the method of applying the polymer to the surface results in a product that is materially different from a product made by some other process. Thus, the new grounds of rejection give no patentable weight to the method by which the polymer layer is formed or applied.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth

in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

### *Election/Restrictions*

To summarize the current election, applicants elected the species where the article is an orthopedic implant, the protein-resistant head group is tri(sarcosine), and the surface portion comprises metal.

Claims 3, 15, 20, 22-27, 52, and 54-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

### *Claim Objections*

Claims 28 and 51 are objected to because of the following informalities: the claims recite ""contact said article to a biological fluid". The word, "to", should be "with" in order to be more grammatically correct. Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The four factual inquiries of Graham v. John Deere Co. have been fully considered and analyzed in the rejections that follow.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. (previously cited) view of Hawker et al. (previously cited), Ishihara et al. (Colloids and Surfaces B;

Biointerfaces 2000 18:325-335), Morgan (previously cited), Allbritton et al. (previously cited), and Leckband et al. (previously cited).

Broadly, the invention claimed is a method of using a device (article) with a coating of polymer brushes on its surface that are attached to the device surface via a linking layer. These polymer brush bristles have protein resistant groups (kosmotropes) that confer protein resistance to the surface of the device. Chapman et al. teach this concept where their coating resists protein and bacterial adhesion (see figure 1 and paragraphs 114-117; instant claim 1). A self-assembled monolayer of alkanethiol is formed on an article that is coated with gold (see paragraph 153 and 159; instant claims 2, 4 and 6). The exposed end is converted into a reactive functional group (initiator terminated alkanethiol) such that a polymer can be grafted (see paragraphs 101 and 153; instant claim 7). This polymer contains several head groups (branches) that resist the adsorption of proteins and bacteria (see paragraph 101, 153, and 162). This yields a surface coating of protein resistant polymer brushes. Chapman et al. teach such coatings for articles that are in-dwelling, such as artificial bone or joint replacements (orthopedic implant) (see paragraph 64; instant claim 21). Chapman et al. also teach self-assembled monolayers that display different protein and bacteria resistant head groups. Tri(sarcosine) is in the set demonstrated to be particularly effective (see figures 4-5 and paragraph 144; instant claims 12-14). Chapman et al. go on to teach that in addition to protein and bacteria resistance, their polymer layers can be further modified by covalently attaching ligands that bind specific biomolecules (see paragraph 124; instant claim 18-19). Protein molecules as well as peptides are particularly envisioned

as these ligands (see paragraph 121; instant claim 18). Since a receptor is a chemical structure that provides a site of attachment, these envisioned proteins qualify as receptors (see instant claim 19). Upon exposure to fluid with biomolecules, adsorption of general biomolecules (e.g. protein) and bacteria is resisted such that binding of those biomolecules for which the ligand is specific occurs (see paragraph 124; instant claim 32). The *in vivo* contacting of the device of Chapman et al. with biological fluids is clearly envisioned in their contemplation of in-dwelling medical devices as substrates for their taught coating (see paragraph 42). This reference does not explicitly teach the claimed polymer brushes with tri(sarcosine) head groups that the orthopedic implant is a dental prosthesis, that the polymer is formed of monomers with a vinyl core monomer group and a protein resistant head group coupled thereto, produced via surface initiated polymerization, or that the linking layer is patterned on the substrate.

Morgan teaches a dental implant with a threaded region that is composed of biocompatible material (e.g., titanium) and anchored into cortical bone (orthopedic implant) (see column 2 lines 28-35; instant claims 21 and 53). The implant is taught to be temporary, remaining implanted for four to six weeks (*in vivo* contacting with blood) (see column 1 lines 55-67; instant claims 28-31 and 51). The lower end of this range meets the limitation of up to approximately 26 days and one month as recited in claims 60-63.

Ishihara et al. teach the modification of a surface to combat its likelihood to induce blood coagulation due to protein adhesion when in contact with blood *in vivo* (see page 326 column 1 lines 1-7 and 22-25). They specifically teach attachment of

polymer chains to the surface by graft polymerization of 2-methacryloyloxyethyl phosphorylcholine (see page 326 column 2 paragraph 1). The result is polymer brushes attached to the surface. Chapman et al. also teach phosphorylcholine as protein resistant head group on surface bound chains, but its performance in this capacity was not as good as tri(sarcosine) (see Chapman et al. figure 5).

Hawker et al. teach polymer brush patterns built from a self-assembled monolayer on a substrate (see abstract; instant claims 38). In particular, a substrate surface that can be composed of a variety of envisioned materials (e.g. gold or tungsten) serves as the base for the polymer (see column 8 lines 9-18). Subsequently a compound (linking layer) containing a group reactive with the substrate surface on one end and providing an initiator on the other end is applied to the surface (see column 8 lines 56-67 and column 9 lines 27-29). The material is then contacted with a polymerizable composition composed of monomers that sequentially form polymers at these initiation sites (see column 9 lines 60-64). One preferred technique utilizes an initiator that generates a free radical polymerization and vinyl monomers (see column 10 lines 10-17; instant claims 9, 28, and 51). The resulting polymers are taught to be between 28 and 38 nm in length (see figure 3; instant claims 16 and 48). This technique is taught in particular in the production of patterned surfaces, where the initiator containing molecules are placed in particular locales on the substrate (see column 8 lines 53-64; instant claims 5 and 37). In one example, Hawker exemplifies the compound that makes up the linking layer as an initiator terminated alkanethiol that

forms a patterned or continuous self-assembled monolayer (column 13 lines 46-50 and 58-63; instant claims 4-7 and 36-39).

Allbritton et al. teach surface grafted polymers to modify the surface of medical devices and confer desired properties (see paragraph 12). Particular monomers that resist protein adhesion are chosen for surface initiated polymerization (see paragraph 42). Allbritton et al. go on to teach various grafting densities for the polymers generated from monomers that include polyethylene glycol monomethoxyl acrylate (see paragraphs 34 and 42). Specifically, grafting densities from approximately 5 $\mu g/cm^2$ (50 $mg/m^2$) to 60 $\mu g/cm^2$ (600 $mg/m^2$) are taught (see figure 4A and paragraph 24; instant claims 28 and 51).

Leckband et al. teach polymer brushes on a substrate as a protein resistant surface (see abstract). In particular, Leckband et al. discuss that the graft density (polymer surface density) is a key parameter in controlling the degree of protein adsorption retardation (see page 1143 paragraph 4). Leckband et al. also teach that this density is optimized based upon the target environment (e.g. size, geometry and concentration of proteins) (see page 1143 paragraph 4).

In view of the teachings of Chapman et al., it would have been obvious to one of ordinary skill in the art at the time of the invention to select tri(sarcosine) as the protein and bacteria resistant head group to include in the surface bound polymer of their invention, where an orthopedic implant is the coated article and an alkanethiol layer linking the polymer to the article substrate. Since the use of a device for its intended purpose is obvious, the contacting of such a device to a biological fluid such that

selective binding can occur to the attached ligands while repelling non-specific adhesion would also have been obvious based upon the teachings of Chapman et al. Since Chapman et al. and Ishihara et al. teach polymer brushes that display particular side chains on medical device surfaces to resist adsorption of undesired biological species upon implantation, it would have been obvious to one of ordinary skill in the art to combine their teachings. Ishihara et al. and Allbritton et al. demonstrate the knowledge of acrylate and methacrylate monomers with various protein resistant functional groups that were used to generate polymer brushes to yield protein resistant surfaces. In addition, it also would have been obvious to combine the teachings of Chapmen et al. and Hawker et al. because both teach surface bound polymeric coatings attached via self-assembled monolayers of reactive alkanethiol groups on metallic surfaces. As a result it would have also been obvious to prepare the polymer brushes suggested by Chapman et al. from a methacrylate functionalized with tri(sarcosine) instead of phosphorylcholine due to its superior protein resistance. Hawker et al. then guides the surface initiated preparation of polymer brushes from these monomers. Further, it also would have been obvious to this ordinarily skilled artisan to select the dental implant of Morgan as an orthopedic implant that would benefit from of the protein resistant coating as taught by Chapman et al. in view of Ishihara et al., Allbritton et al. and Hawker et al. due to its contact with blood once implanted. Based upon these teachings it would have been obvious to one of ordinary skill in the art at the time of the invention to provide the dental implant of Morgan with a layer of polymer brushes having protein resistant functional groups as taught by Chapman et al. via the method of Hawker et al. using a

methacrylate monomer coupled with tri(sarcosine) instead of the phosphorylcholine as taught by Ishihara et al. (see instant claims 44-46). A free radical polymerization initiated from a self-assembled monolayer of initiator-terminated alkanethiols on a gold surface would follow from this combination of references yielding the claimed stem and plurality of branches (see instant claim 28). Further modification of the resulting layer of polymer brush molecules by covalently attaching a protein (ligand), based upon the teachings of Chapman et al., would also have been obvious based on the benefits the teaching from this modification (see instant claims 18 and 50). The implantation of the device, as taught by Morgan, would result in its contacting blood, *in vivo*, for greater than one day and up to 26 days as well as one month where proteins do not bind to the surface. In view of the teachings of Allbritton et al. of polymers with functional groups that were taught by Chapman et al. to function similarly to tri(sarcosine), it would have been well within the purview of one of ordinary skill in the art to optimize the grafting density of the polymer brushes of Chapman et al. in view of Ishihara et al., Hawker et al., and Morgan in order to achieve the desired degree of protein adsorption resistance. The lower end of the grafting density range for the protein resistant polymers falls within the range instantly claimed (see instant claims 28 and 51). Therefore claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 are obvious over Chapman et al. in view of Ishihara et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al.

Claims 8 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. in view of Ishihara et al., Hawker et al., Morgan, Allbritton et al. and

Leckband et al. as applied to claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 above, and further in view of and Kim et al. (Journal of the American Chemical Society 2000 122:7616-7617).

Chapman et al. in view of Ishihara et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al. make obvious the method of instant claim 28 where the monomer has a methacrylate core. This modified reference does not explicitly teach that the polymerization is carried out via atom transfer radical polymerization.

Kim et al. teach that surface initiated polymerization of methacrylate monomers can be successfully conducted via atom transfer radical polymerization (see page 7617 column 2 paragraph 2). Here a self-assembled monolayer of initiator terminated alkanethiols is employed to initiate the reaction from a substrate surface (see Scheme 1). The result is a series of polymer brushes attached to a linking layer on the substrate surface (see page 7616 column 1 paragraph 2).

As a known option within their technical grasp to achieve the same end result, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ atom transfer radical polymerization as the polymerization method instead of free radical polymerization in the invention of Chapman et al. in view of Ishihara et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al. where vinyl monomers are used as the core group. Therefore claims 8 and 28 are obvious over Chapman et al. in view of Ishihara et al., Hawker et al., Morgan, Allbritton et al., Leckband et al., and Kim et al.

*Claim 28 recites a method of using an article having a nonfouling surface where the steps of use require providing an article having a nonfouling surface thereon and contacting this article with a biological fluid where proteins in the fluid do not bind to the surface of the article. Similarly, claim 51 also recites a method of using a product defined as a product-by-process but further recites additional details concerning where the contacting occurs and the nature of the biological fluid. The article is defined by a product-by-process in step (iii). The initiator from the recited polymerization in the product-by-process is not required to remain as part of the linking layer; therefore the article need only have a substrate, a linking layer, and a polymer layer of polymer brushes at a density of from 40 to 100 milligrams per meter$^2$ having a stem and a plurality of branches of protein resistant head groups that can be generated from vinyl monomers with at least one coupled protein resistant head group. In addition, the nature of the polymerization (e.g. atom transfer radical polymerization vs. free radical polymerization) does not inherently impart a particular structure to the polymer, therefore claims 8 and 9 do not add structural limitations to the claims. As a result, the practice of the methods with a product having the structural features implied by the method steps that is made by a different method (e.g., polymer bound to surface vs. surface initiated polymerization) would meet the limitations of these claims. This interpretation is employed in the rejections that follow.*

Claims 2, 4, 6- 9, 11-14, 18-19, 21, 28-31, 51, 53, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. view of Morgan and Allbritton et al.

Broadly, the invention claimed is a method of using a device (article) with a coating of polymer brushes on its surface that are attached to the device surface via a linking layer. These polymer brush bristles have protein resistant groups (kosmotropes) that confer protein resistance to the surface of the device. Chapman et al. teach this concept where their coating resists protein and bacterial adhesion (see figure 1 and paragraphs 114-117; instant claim 1). A self-assembled monolayer of alkanethiol is formed on an article that is coated with gold (see paragraph 153 and 159; instant claims 2, 4 and 6). The exposed end is converted into a reactive functional group (initiator terminated alkanethiol) such that a polymer can be grafted (see paragraphs 101 and 153; instant claim 7). This polymer contains several head groups (branches) that resist the adsorption of proteins and bacteria (see paragraph 101, 153, and 162). This yields a surface coating of protein resistant polymer brushes. Chapman et al. teach such coatings for articles that are in-dwelling, such as artificial bone or joint replacements (orthopedic implant) (see paragraph 64; instant claim 21). Chapman et al. also teach self-assembled monolayers that display different protein and bacteria resistant head groups. The tri(sarcosine) as well as phosphorylcholine are taught where the tri(sarcosine) has much better performance as a repellant to protein adhesion (see figures 4-5 and paragraph 144; instant claims 12-14). Chapman et al. go on to teach that in addition to protein and bacteria resistance, their polymer layers can be further

modified by covalently attaching ligands that bind specific biomolecules (see paragraph 124; instant claim 18-19). Protein molecules as well as peptides are particularly envisioned as these ligands (see paragraph 121; instant claim 18). Since a receptor is a chemical structure that provides a site of attachment, these envisioned proteins qualify as receptors (see instant claim 19). Upon exposure to fluid with biomolecules, adsorption of general biomolecules (e.g. protein) and bacteria is resisted such that binding of those biomolecules for which the ligand is specific occurs (see paragraph 124; instant claim 32). The *in vivo* contacting of the device of Chapman et al. with biological fluids is clearly envisioned in their contemplation of in-dwelling medical devices as substrates for their taught coating (see paragraph 42). In addition, Chapman et al. teach providing a nonfouling article that comprises a substrate surface, a linking layer in the form of a self-assembled monolayer that meets the limitations of comprising initiator terminated alkanethiols. Chapman et al. do not explicitly teach the claimed polymer brushes with tri(sarcosine) head groups attached to a polymer that can be generated from vinyl monomers, the recited surface density for these brushes, that the orthopedic implant is a dental implant, or a particular duration for the *in vivo* contacting period.

Morgan teaches a dental implant with a threaded region that is composed of biocompatible material (e.g., titanium) and anchored into cortical bone (orthopedic implant) (see column 2 lines 28-35; instant claims 21 and 53). The implant is taught to be temporary, remaining implanted for four to six weeks (*in vivo* contacting with blood) (see column 1 lines 55-67; instant claims 28-31 and 51). The lower end of this range

meets the limitation of up to approximately 26 days and one month as recited in claims 60-63.

Allbritton et al. teach surface grafted polymers to modify the surface of medical devices and confer desired properties (see paragraph 12). Particular monomers that resist protein adhesion are chosen for surface initiated polymerization (see paragraph 42). Allbritton et al. go on to teach various grafting densities for the polymers generated from monomers that include polyethylene glycol monomethoxyl acrylate (see paragraphs 34 and 42). Specifically, grafting densities from approximately 5 $\mu g/cm^2$ (50 $mg/m^2$) to 60 $\mu g/cm^2$ (600 $mg/m^2$) are taught (see figure 4A and paragraph 24; instant claims 28 and 51).

Since Chapman et al. and Allbritton et al. teach polymer brushes that display particular side chains on medical device surfaces to resist adsorption of undesired biological species upon implantation, it would have been obvious to one of ordinary skill in the art to combine their teachings. Allbritton et al. demonstrate the knowledge of polymers made from vinyl containing acrylate monomers with protein resistant functional groups that were used to generate polymer brushes to yield protein resistant surfaces. The tri(sarcosine) is taught to function similarly or a bit better than the polyethyleneglycol side chain of Allbritton et al. in its resistance to protein adsorption, therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute tri(sarcosine) for the polyethyleneglycol functional group on the monomers of Allbritton et al. as the substitution of one known element for another to yield a predictable result (see Chapman et al. paragraph 152). Further, it also would

have been obvious to this ordinarily skilled artisan to select the dental implant of Morgan as an orthopedic implant that would benefit from of the protein resistant coating as taught by Chapman et al. in view of Allbritton et al. due to its contact with blood once implanted. Based upon these teachings it would have been obvious to one of ordinary skill in the art at the time of the invention to provide the dental implant of Morgan with a linking layer of self-assembled initiator terminated alkanethiol to which is attached a layer of polymer brushes having protein resistant functional groups as taught by Chapman et al. using an acrylate monomer coupled with tri(sarcosine) instead of the polyethyleneglycol as taught by Allbritton et al. (see instant claims 44-46). The preparation of such a layer with continuous coverage over the surface of this implant would have been obvious in order to provide uniform protection. The selection of a surface density for these polymer brushes at the low end of the range taught by Allbritton et al. also would have been obvious since the tri(sarcosine) side chains were taught to be a bit more effective than those of Allbritton et al. in resisting protein adsorption. Further modification of the resulting layer of polymer brush molecules by covalently attaching a protein (ligand), based upon the teachings of Chapman et al., would also have been obvious based on the benefits the teaching from this modification (see instant claims 18 and 50). Finally, the implantation of the device, as taught by Morgan, would result in its contacting blood, *in vivo*, for greater than one day and up to 26 days as well as one month where proteins do not bind to the surface. Therefore claims 2, 4, 6- 9, 11-14, 18-19, 21, 28-31, 51, 53, and 60-63 are obvious over Chapman et al. in view of Morgan and Allbritton et al.

***Response to Arguments***

The applicants' arguments filed August 29, 2011 have been fully considered but they are not persuasive. Nevertheless, in order to more clearly demonstrate what was appreciated by the prior art, the previous grounds of rejection are hereby withdrawn. Modified forms of the previous rejections are presented above as well as an additional rejection based upon an alternate claim interpretation.

*Regarding the rejection made over Chapman et al. in view of Morgan, Hawker et al., Zhang et al., Allbritton et al., and Leckband et al.:*

The applicants highlight the number of references employed in the rejection. However, the reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

The applicants' arguments concerning Zhang et al. are not persuasive for several reasons. The applicants argue that modification of Zhang et al. is contrary to its teachings where the rejection would require the breakdown of the taught pre-formed polymer into its monomer units. In re *Ratti* is then cited to support this argument who discusses that substantial reconstruction and redesign of the elements in the primary reference of an obviousness rejection pointed to the non-obviousness of the claims. In the instant case, Zhang et al. is not the primary reference that is relied up so the fact

pattern of the instant case and that of the cited case law is not the same. Instead Zhang et al. was employed to highlight a monomer that is well known in the art to be employed to produce polymers and copolymers that are protein resistant due to the presence of its phosphorylcholine side chain. Further, it was known in the art to apply protein resistant materials in several ways on surfaces in order to protect them from undesired adsorption. These include cast films which yield a rather random orientation like that of Zhang et al. and grafting which provides an organized arrangement like that of Chapman et al. The fact that the teachings by Zhang et al. focus on one of these configurations does not mean that their polymer would only be functional in this orientation, particularly since its side chain is so well known for protein resistance. Furthermore, the application of suggested monomers in the polymer of one reference to a similar situation does not require the destruction of the polymer or change the principle operation of the polymer as the applicants suggest in their arguments. The ability of the polymers of Zhang et al. to mimic biological membranes is due to the presence of the phosphorylcholine, not the particular polymer backbone to which it is attached. The application of their monomers to another surface or another polymer in no way destroys the function of polymer's protein resistance. Nevertheless, in the interest of further demonstrating that the prior art appreciated the concept of a layer of polymer brushes having protein resistant head groups along their length, Ishihara et al. has been cited in place of Zhang et al.

The applicants argue that Chapman et al. is not directed to brush polymers because pre-formed polymer are attached to their self-assembled monolayers on gold and are then coupled with protein resistant head groups. Brush polymers are known in the art as polymers that are attached at one end to a substrate thereby creating a series of bristles on the substrate surface. Even if a slightly different interpretation is employed and the bristles of the brush are considered to be the protein resistant side-chains along the "handle" created by the polymer backbone that is attached at one end to the substrate, the teachings of Chapman et al. teach such a polymer architecture. Whether the polymer is formed then attached to the substrate or polymerized directly from the substrate, it would still have the same architecture and the chains would be arranged in the same way across the substrate surface. Both Chapman et al. and the instant claims recite polymers with at least one protein resistant head group along a backbone that is covalently bound at one end to a substrate via a self-assembled linking layer. These teachings meet the limitations of polymer brushes. Chapman et al. suggests polymers in general that contain functional groups which resist protein adhesion as being attached to their self-assembled linking layer. This directs the artisan of ordinary skill to select polymers that fit this requirement. Other prior art references, as detailed in the rejections, point to polymers generated from vinyl monomers that perform in this capacity. Allbritton et al. provides the teaching of known surface densities of protein resistant polymer brushes to fill this void in the teachings of Chapman et al. Thus in combination the cited references render the instant invention obvious.

Additionally, the applicants argue that there is no suggestion that the functional groups of Chapman et al. would work in the method of Hawker et al. While Chapman et al. teach particular embodiments of their invention, they also teach a covalently bonded layer of polymer on a substrate surface having functional groups to make the surface resistant to protein adsorption. They exemplify a poly(ethylene imine) polymer that is functionalized with protein resistant head groups after it is bound to the surface, but Chapman et al. go on to suggest that other polymers can be bonded to the surface and reach the same end. The teachings of Hawker et al. direct the artisan of ordinary skill to prepare polymer brushes by grafting (polymerizing) the polymer from the surface instead of grafting the per-formed polymer to the surface. There is no reason highlighted by the applicants to suggest that the side chains of Chapman et al. would interfere with this grafting from" process. In fact Allbritton et al. teach a "grafting from" method of generating polymer brushes that employ monomers having a polyethylene side chain, which is a longer version of one of the functional groups of Chapman et al.

The applicants go on to offer arguments against two references that were combined in the rejection stating that Chapman et al. in combination with Hawker et al. do not render the invention obvious. However when these two references are considered in light of rest of the references cited in the rejection, the invention is rendered obvious. There are two methods of covalently attaching polymers to substrates, Chapman et al. teach one, "grafting to", where the polymer is formed then attached to the surface and Hawker et al. teaches the other, "grafting from" where the polymer is polymerized directed from the surface. There is no explicit teaching in

Chapman et al. that their method of attaching the polymer to a surface must be employed in order to be in accordance with their invention. Thus a "grafting from" methodology where polymers having protein resistant side chains are polymerized from the self-assembled monolayer of Chapman et al. is in accordance with their method and would have been obvious from the combination of the full set of cited references. In contrast to the applicants' argument, the addition of an acrylate monomer coupled with tri(sarcosine) to the combination of Chapman et al. with Hawker et al., as the rejection suggests, would in fact lead to polymer brushes as claimed. The addition of Morgan, Allbritton et al. and Leckband et al. to this combination of teachings remedies the deficiencies of Chapman et al., Hawker et al., and Ishihara et al. in their teachings of dental implants as orthopedic implants and the surface density of protein resistant polymer brushes to employ on a surface.

The applicants go on to argue that Allbritton et al. teach graft polymer and not brush polymers. This is not correct. Allbritton teach surface grafted polymers which are the same as brush polymers. Their difference in terminology does not make the arrangement of the polymers different. Allbritton et al. explicitly teach modifying the properties of surfaces by graft polymerization of polymers with desirable properties to the surface (see paragraph 12). This is a type of surface initiated polymerization since initiating species are on the surface that is to be modified. Chapman et al. in view of Hawker et al. already teach the claimed linking layer which the applicants also argue is missing from the teachings of Allbritton et al.

Further the applicants argue that the discussion presented by the examiner was factually incorrect regarding the covalent attachment of the polymers of Allbritton et al. via ultraviolet graft polymerization and its similarity to surface initiated polymerization. First, the exact means by which the polymers of Allbritton et al. are attached to the surface does not influence the validity of their teachings of polymer brush density or its ability to be combined with the other cited references. Second, the process of ultraviolet graft polymerization in Allbritton et al. generates radical species at the surface of the substrate which initiate polymerization of the polymers such that they are covalently bound at the substrate surface. It yields polymer brushes on the substrate surface. This is a surface initiated polymerization and similar to polymerizations that immobilize an initiator to the surface of a substrate. Here again, this initiating species serves to initiate polymerization of the polymers such that they are covalently bound at the substrate surface. The two processes have more than a single point of similarity, as the applicants suggest, and the reliance on the teachings of Allbritton et al. to inform the selection of a surface density of protein resistant polymer brushes would have been an obvious choice for the artisan of ordinary skill due to this similarity.

Since Zhang et al. is no longer cited, the applicants' additional arguments regarding a lack of expectation of success based upon this reference are moot.

The cited references do far more than merely suggest the exploration of a field of experimentation as the applicants argue. Chapman et al. establish that the prior art recognized the benefit of a nonfouling surface with a linking layer composed of a self-assembled monolayer of alkanethiols whose terminal groups serve as the initiation

points for polymer brushes that display a plurality of tri(sarcosine) groups that resist protein adsorption for the surface of devices that contact blood *in vivo*. The generation of such polymer brushes via surface initiated polymerization from these self-assembled monolayers of initiator was taught by Hawker et al. It was also known as a functionally equivalent method for generating the polymer brushes from the highly spatially controllable monolayers. Prior art, as demonstrated by Ishihara et al. and Allbritton et al., also demonstrated the well-known use of acrylate based backbones in polymer brushes that display protein resistant functional groups along their length and are employed to confer protein resistance to surfaces. Allbritton et al. also show that suitable densities for these polymer brushes were known in the art. The rejection does not present an exploratory mission, but instead details that the prior art at the time of the invention was sufficient to direct the artisan of ordinary skill to the method that is instantly claimed. Thus the instant claims are obvious in light of the prior art.

*Regarding the rejection made over Chapman et al. in view of Morgan, Hawker et al., Zhang et al., Allbritton et al., Leckband et al., and Guan et al.*

The applicants argue that because Guan et al. discus polymerization in solution they do not teach polymer brushes. The teachings of Chapman et al. in view of Morgan, Hawker et al., Ishihara et al., Allbritton et al., and Leckband et al. teach polymer brushes as required by the claims. The method of surface initiated polymerization taught by their combination of references is free radical polymerization due to a free radical initiator being attached to the alkanethiol in the self-assembled monolayer of the linking layer.

Since free radical and atom transfer polymerization were both known to successfully polymerize vinyl monomers based upon the initiator and reaction conditions employed, there would have been good reason to expect that if free radical polymerization could be conducted from surface bound initiators, atom transfer radical polymerization (ATRP) could as well. Kim et al. has now been cited in place of Guan et al. to demonstrate that the use of ATRP to perform surface initiated polymerization of methacrylate monomers coupled with tri(sarcosine) would have been expected to generate polymer brushes as instantly claimed.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARALYNNE HELM whose telephone number is (571)270-3506. The examiner can normally be reached on Monday through Friday 9-5 (EDT).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Caralynne Helm/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner
Art Unit 1615